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Review Article

Medical treatment for adenomyosis and/or adenomyoma

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ABSTRACT

Uterine adenomyosis and/or adenomyoma is characterized by the presence of heterotopic endometrial glands and stroma within the myometrium, >2.5 mm in depth in the myometrium or more than one microscopic field at 10 times magnification from the endometrium–myometrium junction, and a variable degree of adjacent myometrial hyperplasia, causing globular and cystic enlargement of the myometrium, with some cysts filled with extravasated, hemolyzed red blood cells, and siderophages. Hysterectomy is a "gold standard" and definitive therapy for uterine adenomyosis, and many cases of adenomyosis have been diagnosed by pathological review retrospectively. As such, the diagnosis of adenomyosis is difficult, and this subsequently results in difficulty in the management of these patients, especially those who are symptomatic but have a strong desire to preserve their uterus. In our previous review, we found that the use of uterine-sparing surgery in the management of uterine adenomyosis and/or adenomyoma is still controversial, although some data support its feasibility. Conservative treatment is still needed in the group of patients that requires preservation of fertility and improvement of quality of life. However, studies focusing on the topic of medical treatment for adenomyosis are rare. In this article, current knowledge regarding the use of medical therapy for uterine adenomyosis, partly based on the understanding of endometriosis, is reviewed.

Introduction

Uterine adenomyosis was first reported in the 19th century and early 20th century; von Rokitansky [1] described it in 1860 and Frankl [2] later defined it as adenomyosis interna. Since then, the general clinical, pathological, and radiologic findings and potentially useful management methods have been reviewed in many studies [3–16], including ours [17,18]. Feldele et al. [9] commented that conservative surgical treatment is impracticable as it is not possible to isolate the adenomyotic tissue adequately; therefore, the authors suggested that hysterectomy is the only rational and complete procedure. In our previous review [17], we found that there is more evidence supporting the advantages of conservative uterine-sparing surgery in providing not only more effective symptom relief but also longer durable symptom control for symptomatic women with uterine adenomyosis and/or adenomyoma, compared with medical treatment alone. Furthermore, the effectiveness of conservative uterine-sparing surgery for adenomyosis was also promising, since the main problem secondary to

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uterine adenomyosis, dysmenorrhea, can be improved significantly, by up to 80%; menorrhea was also improved in more than two-thirds of patients after type I uterine-sparing surgery (complete resection of adenomyosis, also called adenomyomectomy), and half of the patients saw benefit in symptom control after type II conservative uterine-sparing surgery (conservative cytoreductive uterine-sparing surgery) [18]. In addition, there was no negative impact on reproductive performance after conservative uterine-sparing surgery, and, in fact, reproductive performance seemed to be improved compared with that after medical treatment; not only was there a higher cumulative pregnancy rate, but also a higher cumulative final successful delivery rate. That is why Vercellini et al. [19] commented that lesion eradication is a fertility-enhancing procedure. However, there is no doubt that the data supporting the above-mentioned benefits for symptomatic women with uterine adenomyosis after conservative uterine-sparing surgery are limited, suggesting that the benefit may be moderate. In fact, one of the main indications for surgery is temporary pain relief in women seeking spontaneous conception. In addition, the effect of surgery on pain is usually only temporarily satisfactory, and the risk of complications varies according to the type of lesion extirpated. In light of this, greater understanding of the pathophysiology of adenomyosis might be very important, and might help us manage these patients in the future.

Pathophysiology of adenomyosis

The need for hysterectomy to diagnose adenomyosis means that many cases go undetected, and limits our understanding of the prevalence and clinical impact [20]. There is no agreement that the histological diagnosis can be made, since the depth of myometrial invasion ranges from 0.5 cm to >25% of the myometrial thickness in one high power field, although adenomyosis-related symptoms may not correlate with the depth of invasion [21]. In addition, there is no universally accepted classification of adenomyosis, even though Reinhold et al. [22] defined the criteria as the presence of endometrial tissue at $\geq$ 2.5 mm below the endomyometrial junction and a thickness of the junction zone of $\geq$12 mm. Brosens et al. [23] suggested that adenomyosis is a dichotomous disease that is characterized by disruption of the inner myometrial architecture and function, with secondary infiltration of endometrial elements into the myometrium. As early as 2002 [24], we attempted to analyze genetic aberrations in uterine adenomyosis using comparative genomic hybridization; however, we failed to detect any significant genomic amplification or deletion. The possible causes include difficulties specifically related to adenomyosis: that the tissue studied was complicated by a mixture of epithelial and stromal cells in addition to normal myometrial tissue. In addition, there may have been a surplus of normal myometrial tissue in the prepared tissue vs. the adenomyosis tissue. We suggested that special procedures, such as laser-assisted microdissection, and appropriate amplification of DNA by degenerate oligonucleotide-primed polymerase chain reaction, may offer the opportunity to investigate sequence copy number changes in small, morphologically well-defined groups of lesions [24]. Of course, the predominantly normal karyotype seen in adenomyosis may be due to the resolution limits of karyotyping, with any changes present being submicroscopic. The years have passed, and recent evidence supports adenomyosis, which includes an abnormal gene expression, increased angiogenesis and proliferation, decreased apoptosis, impaired cytokine expression, local estrogen production, resistance to progesterone, and increased nerve density, immunological stress, and oxidative stress [20]. Today, the real challenge is tailoring treatment to personal needs, depending on the type and extent of disease. The following sections are a summary of the recent knowledge of useful medications and results for patients with adenomyosis and/or adenomyoma after medical treatment.

Medical treatment

Medical treatments for adenomyosis always follow the principles of the management of endometriosis, which are usually aimed at reducing the production of endogenous estrogen or inducing endometrial differentiation with progestins. Clinical evidence points to the clear and deleterious effect of uninterrupted ovulatory cycles on the development and persistence of adenomyosis; symptoms of adenomyosis usually appear after menarche and vanish after menopause. The objectives of medical treatment are the inhibition of ovulation, abolition of menstruation, and achievement of a stable steroid hormone milieu, based on the concept that the responses of the eutopic and ectopic endometria are substantially similar [19]. Medical therapies commonly used in the treatment of adenomyosis, similar to those for endometriosis, are mainly based on the fact that the hypothalamic–pituitary–gonadal axis plays a pivotal role in every phase of mammalian reproduction, and include gonadotropin-releasing hormone agonist (GnRH agonist), oral contraceptives (OCs), progestins, danazol, and recently, selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs) or aromatase inhibitors (AIs). These agents create a hypoestrogenic (GnRH agonists, AIs), hyperandrogenic (danazol, gestrinone), or hyperprogestogenic (OCs, progestins) environment, with suppression of endometrial cell proliferation [19]. However, medical treatments are symptomatic and not cytoreductive: lesions survive the use of any drug, at any dose, for any length of time, and are ready to resume their metabolic activity at treatment discontinuation [19]. Medical treatments may represent standard therapies for adenomyosis and are associated with adverse events impacting long-term use and adherence. Since no medical treatment for endometriosis is universally effective, we should emphasize that this concept is also applicable to adenomyosis therapy. Therefore, parts of the following data are based on studies of endometriosis.

SERMs

Basic clinical studies indicate major roles for estrogen and progesterone in the pathology of adenomyosis. Our previous study proposed that the estrogen-induced epithelial–mesenchymal transition (EMT) in endometrial epithelial cells contributes to the development of adenomyosis based on the following evidence: (1) E-cadherine was downregulated and vimentin was upregulated in the epithelial compartment of adenomyotic lesions; (2) changes in EMT markers were associated with the serum estradiol (E2) levels; (3) estrogen induced EMT migration, and invasion of estrogen receptor (ER)-positive endometrial cells, and such effects were abrogated by a SERM; and (4) estrogen-dependent adhesion of xeno-transplanted endometrial fragments to the peritoneal cavities of mice was observed, suggesting that SERMs may be a potential therapeutic agent for adenomyosis patients [25]. The finding that SERMs [26–30], including clomiphene, tamoxifen, toremifene, raloxifene, ospemifene, lasofoxifene, bazedoxifene, and bazedoxifene/conjugated estrogen, have tissue-specific agonist–antagonist activity led to the realization that the classic model was incomplete and that estrogen action was more complex than had been thought. The mechanisms of the tissue-selective, mixed agonist–antagonist action of SERMs can be explained by three interactive mechanisms, including differential ER expression in a given target tissue, differential ER conformation on ligand binding, and differential expression and binding to the ER coregulator proteins (Table 1),

Table 1
Mechanisms of candidate drugs for treatment in women with endometriosis and/or adenomyosis.

Drugs	Mechanisms
Selective ER modulator (tamoxifen, toremifene, raloxifene, ospemifene, lasofoxifene, and bazedoxifene)	(1) Differential ER expression in a given target tissue (2) Differential ER conformation on ligand binding (3) Differential expression and binding to the ER coregulator proteins
ER inhibitor (fulvestrant)	Complete blockade of estrogen action, resulting in impaired dimerization, increased turnover, and disrupted nuclear localization
Selective PR modulator (ulipristal acetate, mifepristone, asoprisnil, lonaprisan, telapristone acetate, PRA-910, ZK 136799, and onapristone)	(1) Differential PR expression in a given target tissue (2) Differential PR conformation on ligand binding (3) Differential expression and binding to the PR coregulator proteins
Progestins	Action involves decidualization and subsequent atrophy of endometrial tissue
Gestrinone	(1) A progestational withdrawal effect at the endometrial cellular level (2) Inhibition of ovarian steroidogenesis
Aromatase inhibitor	Inhibition of the estradiol synthesis Type I: suicidal or noncompetitive Type II: competitive
Oral contraceptives	(1) Decrease of retrograde menstruation (the maximal effect occurs when given continuously) (2) Induction of a pseudo-pregnant status, which causes decidualization and subsequent atrophy of the endometrium
Danazol	Androgenic and hypoestrogenic environment
Levonorgestrel-releasing intrauterine system	May be mediated through a slow-release progestin
Gonadotropin-releasing hormone agonists	Downregulation of gonadotropin releasing hormone

ER = estrogen receptor; PR = progesterone receptor.

which are considered a potentially effective therapy for women with adenomyosis [31–33]. In a mouse model, SERM-treated animals consistently demonstrated decreased endometriosis lesion size compared to vehicle-treated animals [34]. In addition, macroscopic analysis showed that there were no signs of active endometriotic implants in SERM-treated animals, and histological examination showed diminished glands and a decrease in luminal cell height as a consequence of SERM treatment [34]. For the treatment of adenomyosis, the ideal SERM might be one that has antagonistic activity in the endometrium (adenomyotic lesion) and agonistic activity for bone and lipids [26,27]. Stratton and colleagues [35] pioneered the evaluation of whether 6 months of SERM was effective in treating chronic pelvic pain in women with endometriosis, but the Data Safety Monitoring Committee terminated the study early when the SERM group experienced pain ($p = 0.03$) and had a second surgery ($p = 0.16$) significantly sooner than the controls. However, biopsy-proved endometriosis was not associated with the return of pain ($p = 0.6$), suggesting that other factors are implicated in pelvic pain [35]. Further studies using SERMs and possibly other medical therapies may identify an ideal agent for the treatment of adenomyosis.

SPRMs or progestins

The role of progesterone in the development or persistence of adenomyosis is not clear for the following reasons: (1) the protective role of progesterone in endometrial cancer [36,37] is not completely applicable to adenomyosis, since adenomyosis is not pure epithelial proliferation but rather increased inflammation and cell survival due to diminished apoptosis or differentiation; (2) progesterone induces a transient proliferation of stromal cells in normal endometrium; (3) only half of patients with adenomyosis benefit from progesterone therapy; (4) antiprogestins with mixed agonist and antagonist properties (SPRM) reduce adenomyosis-associated pelvic pain, possibly more effectively than progestins; although the reason is not clear, it may be secondary to progesterone resistance in adenomyosis; and (5) adenomyotic lesions produce significant quantities of progesterone and contain strikingly lower levels of progesterone receptor (PR) with endometrium [38,39]. SPRMs interact with the PR, allowing the binding of PR dimers to target gene promoters [38–43]. Similar to SERM on ERs, the conformation induced by each SPRM promotes the interaction of PR with both coactivators and corepressors (Table 1), leading to mixed agonist–antagonist activity depending on their structure and the relative tissue concentrations of these comodulators. Evidence has shown that SPRMs, including ulipristal acetate, mifepristone, asoprisnil, lonaprisan, telapristone acetate, PRA-910, ZK 136799, and onapristone, inhibit endometrial proliferation or suppress adenomyotic lesions, resulting in inhibition of prostaglandin production and endometrial atrophy in animal models [40]. In addition, a small number of clinical studies have also demonstrated that SPRMs have potential in the treatment of adenomyosis. For example, taking 50-mg of mifepristone daily has been shown to improve pain and cause regression of adenomyosis [41], asoprisnil and telapristone acetate have also been reported to relieve adenomyosis-associated pain [42,43], suggesting that these beneficial effects of SPRM treatment may reflect changes in the endometrial morphology and/or the absence of bleeding, although the potential consequences of SPRM-associated endometrial change remain unknown and the effect of long-term treatment with SPRMs needs further determination.

Progestins and antiprogestins (gastrinone)

A Cochrane database systematic review showed that the progestagen or progesins medroxyprogesterone acetate (100 mg medroxyprogesterone (MPA) daily) appeared to be more effective at reducing all symptoms up to 12 months of follow-up (mean difference −0.70, 95% confidence interval −8.61 to −5.39; $p < 0.00001$) compared with placebo (moderate-quality evidence) [44,45]; however, there was evidence of significantly more cases of side effect, such as acne and edema in the MPA group compared with placebo [44]. Norethisterone acetate (2.5 mg per day) is associated with a marked degree of pain relief and satisfaction with treatment after 1 year, although the efficacy seems to be more gradual, but progressively better with a longer duration of use [19]. A drawback of progestin therapy is the reduction of libido in about one-fifth of women [19]. Compared with other medical treatment, amenorrhea and bleeding were more frequently reported in the progestin group; in addition, the depot progestagen group experienced significantly more adverse effects [44]. All suggest that only limited evidence to support the use of progestagens for

endometriosis- and adenomyosis-associated pain [44] and the randomized clinical trials addressing quality of life had a high withdrawal rate [45]. Gestrinone (ethylnorgestrienone, R2323) is an antiprogestational steroid used in Europe and Taiwan for the treatment of endometriosis, which is administered orally with doses ranging from 2.5 mg to 10 mg, administered daily to weekly [46]. The mechanism of action includes a progestational withdrawal effect at the endometrial cellular level and inhibition of ovarian steroidogenesis [46]. Side effects relate to both androgenic and antiestrogenic effects, and there was no evidence of a benefit of gestrinone compared with danazol [44]. In addition, the therapeutic effects of gestrinone for dysmenorrhea were significantly worse than those of GnRH agonist [44].

AIs

Aromatase is the enzyme responsible for the transformation of androgens, androstenedione, and testosterone, into estrogens, estrone, and E2, respectively [47]. Aromatase enzyme is comprised of two polypeptides, a specific cytochrome P450 (product of the CYP19 gene), and flavoprotein, nicotinamide–adenine dinucleotide phosphatate cytochrome P450 reductase [48]. Aromatase is an excellent target for inhibition of the E2 synthesis because it is the final step in steroid biosynthesis; therefore, there are no important downstream enzymes to be affected. Due to the molecular observations of increased expression of aromatase P450 in adenomyotic lesion published during the past 10 years, the number of clinical trials employing AIs in the management of endometriosis and/or adenomyosis has increased strikingly since 2004 [49,50]. AIs are classified into type I inhibitors (suicidal or noncompetitive) and type II inhibitors (competitive), and both compete for binding to the active site [48]. Once a type I inhibitor has worked, the enzyme initiates hydroxylation, producing an unbreakable bond between the inhibitor and the enzyme protein, resulting in permanent blockage; type II inhibitors work in a reverse manner on the active enzyme site without triggering enzyme activity. However, the inhibition can disassociate from the binding site, allowing renewed competition between the inhibitor and the substrate for binding to this active site; therefore, a constant presence of the type II inhibitor is needed to continue the effect, and the effectiveness depends on the affinities of the inhibitor and the substrate [48]. Ferrero et al. [51] performed a systematic review to assess the efficacy of AI in treating endometriosis-related pain, especially focusing on type II nonsteroidal AI, such as anastrozole and letrozole, and analyzed a total of 251 women from 10 studies, including five prospective noncomparative studies, four randomized controlled trials, and one patient preference study. All the observational studies demonstrated that AIs combined with either progestins or OC reduced the severity of endometriosis-related pain and improved quality of life; however, some studies showed a high incidence of adverse effects and no improvement of patient satisfaction, or a recurrence of symptoms after discontinuation of treatment, suggesting future investigations should clarify whether the long-term administration of AIs is superior to currently available medical therapies in terms of improvement of pain, adverse effects, and patient satisfaction [51].

OCs

The reasons for using OC in the management of adenomyosis include: (1) a decrease in retrograde menstruation (the maximal effect occurs when given continuously); and (2) induction of a pseudo-pregnant status, which causes decidualization and subsequent atrophy of the endometrium [19]. All OCs have been associated with an increased risk of venous thrombosis, and the effect size depended both on the progestins used and the dose of ethinyl E2, suggesting that combining different preparations of OC into generations of progestogens may not be an appropriate way to prevent the risk of thrombosis [52]. In addition, no differences have been demonstrated between various OCs, and this has led to the use of preparations with the least possible estrogen content to prevent adverse events. Monophasic, low-dose OC shows overall safety, good efficacy, appreciable tolerability and low cost, and may be the best choice for adenomyosis-related pain (dysmenorrhea); continuous use is suggested, with the aim of abolishing uterine flows [19]. Medical therapy with OC enables satisfactory long-term pain control in two-thirds of women with symptomatic endometriosis and/or adenomyosis [19]. Combined OC increased irregular uterine bleeding (60% vs. 26%) and nausea (24% vs. 0%) compared with placebo [45].

Danazol

Danazol is an isoxazol derivative of 12 α-ethinyl testosterone, and has a complex mechanism of action involving inhibiting steroidogenesis, lowering the mid-cycle luteinizing hormone surge, and increasing serum free testosterone levels [53]. Danazol use results in an androgenic and hypoestrogenic environment; the former might have a more direct effect on adenomyotic lesions and reduce pain during and after therapy, and the latter may have an indirect effect on adenomyotic lesions [53], contributing to relieving pain and resulting in clinical improvement in 55–93% of women treated for 6 months [54]. However, danazol and gestrinone are not suitable for prolonged use, partly because of their androgenic side effects, including seborrhea, hypertrichosis, and increased body weight, and the risk of metabolic syndrome, such as their unfavorable effects on serum cholesterol lipoprotein distribution (decreased high-density lipoprotein and increased low-density lipoprotein).

Levonorgestrel-releasing intrauterine system

Although the levonorgestrel-releasing intrauterine system (LNG-IUS) is not Food and Drug Administration-approved for the treatment of endometriosis-related pain, evidence supports its use as an effective alternative treatment, since it abolishes menstruation in one-third of women and substantially decreases the amount of bleeding in another third [19]. One longitudinal contraception study evaluated the prevalence and severity of dysmenorrhea after the use of different kinds of intrauterine contraception methods and the data showed that use of a copper intrauterine device did not influence the severity of dysmenorrhea, but the LNG-IUS was shown to reduce the severity of dysmenorrhea significantly; the study did not provide information on the diagnosis or treatment of endometriosis and adenomyosis, but suggested the efficacy of LNG-IUS in reducing dysmenorrhea [55]. In addition, a recent review offered the good news that physicians have an array of viable treatment options available to treat the distressing condition of heavy menstrual bleeding, which is often secondary to uterine adenomyosis [56]. LNG-IUS reduces abnormal uterine bleeding secondary to endometrial dysfunction more than OC, luteal-phase oral progestins, or nonsteroidal anti-inflammatory drugs, and that antifibrinolytics are more effective than placebo [57]. In addition, one randomized clinical trial found no significant difference between LNG-IUS and the depot gonadorelin analog, leuprorelin in reduction of visual analog scale (VAS) for endometriosis- and/or adenomyosis-related pain throughout the 6 months' treatment (post-treatment change in VAS scores not specified; $p > 0.600$ for the difference in VAS change) [58].

Table 2
Summary of outcomes of women with adenomyosis and/or adenomyoma after medical treatment.

Drugs	Symptom control[a]	Adverse events
SERM	Unsatisfactory	Well-tolerated, hot flush, leg cramp, hypercoagulation status
SPRM	Good to excellent	Well-tolerated, headache, nausea, fatigue and dizziness
Progestins	Good to excellent	Irregular bleeding, nausea/vomiting, mood swings, hot flush, increased body weight
Gestrinone	Good	Seborrhea, hypertrichosis, and increased body weight, and the risk of metabolic syndrome, such as unfavorable effects on serum cholesterol lipoprotein distribution
AI	Unsatisfactory to fair	Frequent and intolerable hypoestrogenic side effects, including vasomotor syndrome, genital atrophy and mood instability, and a negative impact on bone health, also possible bad influence on cardiovascular health
OC	Good to excellent	Irregular bleeding, hypercoagulation status, nausea/vomiting, headache
Danazol	Good to excellent	Seborrhea, hypertrichosis and increased body weight, and the risk of metabolic syndrome, such as unfavorable effects on serum cholesterol lipoprotein distribution
LNG-IUS	Excellent	Irregular bleeding, abdominal pain
GnRH-a	Excellent	Frequent and intolerable hypoestrogenic side effects, including vasomotor syndrome, genital atrophy and mood instability, and a negative impact on bone health, also possible bad influence on cardiovascular health

AI = aromatase inhibitor; GnRH-a = gonadotropin-releasing hormone agonist; LNG-IUS = levonorgestrel-releasing intrauterine system; OC = oral contraceptives; SERM = selective estrogen receptor modulator; SPRM = selective progesterone receptor modulator.
[a] Symptom control: unsatisfactory (exacerbation or improvement <25%); fair (improvement 25–50%); good (improvement 50–75%); and excellent (improvement >75%).

GnRH agonists

Since the hypothalamic–pituitary–gonadal axis plays a pivotal role in every phase of mammalian reproduction, and is also the main cause of uterine adenomyosis, GnRH agonists are target drugs for the treatment of adenomyosis. The GnRH decapeptide was isolated and its structure elucidated in 1971 [59]. Amino acid substitutions have revealed the significance of specific regions for stability, receptor binding and activation of the pituitary gonadotrophs, and modifications mainly at positions 6 and 10 gave rise to analogs with increased potency, extending the half-life from minutes to hours and raising the binding capacity more than 100-fold [59–62]. GnRH agonists are very effective against adenomyosis-related pain, and thereby also contribute to the occurrence of many successful pregnancies and live deliveries [63–67]. However, the use of GnRH agonists is associated with frequent and intolerable hypoestrogenic side effects, including vasomotor syndrome, genital atrophy, and mood instability; it also has a negative impact on bone health and a possible negative influence on cardiovascular health. In addition, GnRH agonists might be the most costly medications available for the treatment of adenomyosis. To minimize the GnRH agonist-inducing adverse events, an add-back therapy with various kinds of hormone preparations has been successfully used recently and enables an indefinite extension of the GnRH agonist treatment period. However, overall costs have continued to increase. Therefore, some authors suggest that GnRH agonist plus add-back therapy is used only in highly selected women unresponsive to other medications or in surgically high-risk patients.

ER inhibitor

Fulvestrant (Faslodex; AstraZeneca, London, UK), a potent pure antiestrogen with high affinity binding with ER, was approved by the US Food and Drug Administration in 2002 for the treatment of hormonal receptor positive metastatic breast cancer [68]. Fulvestrant completely attenuates the ability of the ER to activate or inhibit transcription in a ligand-dependent or independent manner, resulting in a blockade of estrogen action. Although a Phase-II trial on the use of fulvestrant for treating endometriosis was launched, there are no published data yet, suggesting that the trial was terminated, probably due to an efficacy issue or unacceptably high risk/benefit ratio [68]. Guo and Olive [68] suggested that: (1) it is necessary to better understand the mechanisms of endometriosis (adenomyosis) pathogenesis through more basic research; and (2) human endometriosis (adenomyosis) trials have different endpoints than animal studies.

Conclusion

For adenomyosis, the goal of therapy is important, and can include symptom relief and possibly increased fertility. The results of systematic literature reviews have consistently demonstrated that, as long as amenorrhea is obtained, there are no statistical differences between the various available drugs in terms of pain relief, but tolerability, side effects, and costs vary widely [19]. The therapeutic goal of medical treatment is not lesion resorption: lesions survive any drug, at any dose, for any period of use, and come back at treatment discontinuation. Therefore, we should not consider an inefficacy of hormonal manipulation at drug discontinuation. In addition, agents available for the management of adenomyosis are mediated by creating a hypoestrogenic (GnRH agonists, AIs), hyperandrogenic (danazol, gestrinone), or hyperprogestogenic (OCs, progestins) environment [69–71], with suppression of the adenomyotic lesion, and are frequently associated with side effects that impact long-term use and adherence (Table 2). Therefore, treatment should be tailored to the specific symptom or special request of the individual patient, as severity of pain may vary in all women with adenomyosis and more importantly, the same type of symptom may have different implications for different women. Future research is worthwhile.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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References

[1] Von Rokitansky K. Ueber uterusdruesen-neubildung. Z Ges Aerzte Wien 1860;16:577–81 [In German].
[2] Frankl O. Adenomyosis uteri. Am J Obstet Gynecol 1925;10:680–4.
[3] Shwayder J, Sakhel K. Imaging for uterine myomas and adenomyosis. J Minim Invasive Gynecol 2014;21:362–76.
[4] Grimbizis GF, Mikos T, Tarlatzis B. Uterus-sparing operative treatment for adenomyosis. Fertil Steril 2014;101:472–87.
[5] Campo S, Campo V, Benagiano G. Adenomyosis and infertility. Reprod Biomed Online 2012;24:35–46.
[6] Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. Hum Reprod Update 2012;18:374–92.
[7] Sun YL, Wang CB, Lee CY, Wun TH, Lin P, Lin YH, et al. Transvaginal sonographic criteria for the diagnosis of adenomyosis based on histopathologic correlation. Taiwan J Obstet Gynecol 2010;49:40–4.
[8] Meredith SM, Sanchez-Ramos L, Kaunitz AM. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis. Am J Obstet Gynecol 2009;201:107.e1–7.
[9] Fedele L, Bianchi S, Frontino G. Hormonal treatments for adenomyosis. Best Pract Res Clin Obstet Gynaecol 2008;22:333–9.
[10] Levgur M. Therapeutic options for adenomyosis: a review. Arch Gynecol Obstet 2007;276:1–15.
[11] Bergeron C, Amant F, Ferenczy A. Pathology and physiopathology of adenomyosis. Best Pract Res Clin Obstet Gynecol 2006;20:511–21.
[12] Kitawaki J. Adenomyosis: the pathophysiology of an oestrogen-dependent disease. Best Pract Res Clin Obstet Gynaecol 2006;20:493–502.
[13] Matalliotakis IM, Katsikis IK, Panidis DK. Adenomyosis: what is the impact on fertility? Curr Opin Obstet Gynecol 2005;17:261–4.
[14] Tamai K, Togashi K, Ito T, Morisawa N, Fujiwara T, Koyama T. MR imaging findings of adenomyosis: correlation with histopathologic features and diagnostic pitfalls. Radiographics 2005;25:21–40.
[15] Wood C. Surgical and medical treatment of adenomyosis. Hum Reprod Update 1998;4:323–36.
[16] Siegler AM, Camilien L. Adenomyosis. J Reprod Med 1994;39:841–53.
[17] Wang PH, Su WH, Sheu BC, Liu WM. Adenomyosis and its variance: adenomyoma and female fertility. Taiwan J Obstet Gynecol 2009;48:232–8.
[18] Horng HC, Chen CH, Chen CY, Tsui KH, Liu WM, Wang PH, et al. Uterine-sparing surgery for adenomyosis and/or adenomyoma. Taiwan J Obstet Gynecol 2014;53:3–7.
[19] Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 2013;10:261–75.
[20] Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Hum Reprod Update 2013;20:386–402.
[21] Sammour A, Pirwany I, Usubutun A, Arseneau J, Tulandi T. Correlations between extent and spread of adenomyosis and clinical symptoms. Gynecol Obstet Invest 2002;54:213–6.
[22] Reinhold C, McCarthy S, Bret PM, Mehio A, Atri M, Zakarian R, et al. Diffuse adenomyosis: comparison of endovaginal US and MR imaging with histopathologic correlation. Radiology 1996;199:151–8.
[23] Brosens JJ, De Souza NM, Barker FG. Uterine junctional zone: function and disease. Lancet 1995;346:558–60.
[24] Wang PH, Shyong WY, Lin CH, Chen YJ, Li YF, et al. Analysis of genetic aberrations in uterine adenomyosis using comparative genomic hybridization. Anal Quant Cytol Histol 2002;24:1–6.
[25] Chen YJ, Li HY, Huang CH, Twu NF, Yen MS, Wang PH, et al. Oestrogen-induced epithelial-mesenchymal transition of endometrial epithelial cells contributes to the development of adenomyosis. J Pathol 201;222:261–270.
[26] Wang PH, Chao HT. A reconsideration of tamoxifen use for breast cancer. Taiwan J Obstet Gynecol 2007;46:93–5.
[27] Lee WL, Cheng MH, Chao HT, Wang PH. The role of selective estrogen receptor modulators on breast cancer: from tamoxifen to raloxifene. Taiwan J Obstet Gynecol 2008;47:24–31.
[28] Lee WL, Chao HT, Cheng MH, Wang PH. Rationale for using raloxifene to prevent both osteoporosiss and breast cancer in postmenopausal women. Maturitas 2008;60:92–107.
[29] Lee WL, Cheng MH, Tarng DC, Yang WC, Lee FK, Wang PH. The benefits of estrogen or selective estrogen receptor modulator on kidney and its related disease-chronic kidney disease-mineral and bone disorder: osteoporosis. J Chin Med Assoc 2013;76:365–71.
[30] Pinkerton JV, Thomas S. Use of SERMs for treatment in postmenopausal women. J Steroid Biochem Mol Biol 2014;142:142–54.
[31] Taylor HS, Osteen KG, Bruner-Tran KL, Lockwood CJ, Krikun G, Sokalska A, et al. Novel therapies targeting endometriosis. Reprod Sci 2011;18:814–23.
[32] Bulun SE, Cheng YH, Pavone ME, Yin P, Imir G, Utsunomiya H, et al. Estrogen receptor-beta, estrogen receptor-alpha, and progesterone resistance in endometriosis. Semin Reprod Med 2010;28:36–43.
[33] Simsa P, Mihalyi A, Kyama CM, Mwenda JM, Fülöp V, D'Hooghe TM. Selective estrogen-receptor modulators and aromatase inhibitors: promising new medical therapies for endometriosis? Womens Health (Lond Engl) 2007;3:617–28.
[34] Kulak Jr J, Fischer C, Komm B, Taylor HS. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology 2011;152:3226–32.
[35] Stratton P, Sinaii N, Segars J, Koziol D, Wesley R, Zimmer C, et al. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. Obstet Gynecol 2008;111:88–96.
[36] Lee WL, Lee FK, Su WH, Tsui KH, Kuo CD, Hsieh SL, et al. Hormone therapy for younger patients with endometrial cancer. Taiwan J Obstet Gynecol 2012;51:495–505.
[37] Cheng MH, Chen JF, Fuh JL, Lee WL, Wang PH. Osteoporosis treatment in postmenopausal women with pre-existing fracture. Taiwan J Obstet Gynecol 2012;51:153–66.
[38] Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr Rev 2005;26:423–38.
[39] Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev 2013;34:130–62.
[40] Bouchard P, Chabbert-Buffet N, Fauser BC. Selective progesterone receptor modulators in reproductive medicine: pharmacology, clinical efficacy and safety. Fertil Steril 2011;96:1175–89.
[41] Kettel LM, Murphy AA, Morales AJ, Ulmann A, Baulieu EE, Yen SS. Treatment of endometriosis with the antiprogesterone mifepristone (RU486). Fertil Steril 1996;65:23–8.
[42] Chwalisz K, Mattia-Goldberg C, Elger W, Edmonds A. Treatment of endometriosis with the novel selective progesterone receptor modulator (SPRM) asoprisnil. Fertil Steril 2004;82:S83–4.
[43] Spitz IM. Clinical utility of progesterone receptor modulators and their effect on the endometrium. Curr Opin Obstet Gynecol 2009;21:318–24.
[44] Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev 2012;3.CD002122.
[45] Ferrero S, Remorgida V, Venturini PL. Endometriosis. Clin Evid (Online) 2010 Aug 13;2010. pii: 0802. PMID: 21418683 [PubMed – in process] (website: http://www.ncbi.nlm.nih.gov/pubmed/21418683).
[46] Practice Committee of American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. Fertil Steril 2008;90(Suppl. 5):S260–9.
[47] Yeh S, Hu YC, Wang PH, Xie C, Xu Q, Tsai MY, et al. Abnormal mammary gland development and growth retardation in female mice and MCF7 breast cancer cells lacking androgen receptor. J Exp Med 2003;198:1899–908.
[48] Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? Fertile Steril 2006;85:1307–18.
[49] Kimura F, Takahashi K, Takebayashi K, Fujiwara M, Kita N, Noda Y, et al. Concomitant treatment of severe uterine adenomyosis in a premenopausal woman with an aromatase inhibitor and a gonadotropin-releasing hormone agonist. Fertil Steril 2007;87:1468.e9–1468.e12.
[50] Badawy AM, Elnashar AM, Mosbah AA. Aromatase inhibitors or gonadotropin-releasing hormone agonists for the management of uterine adenomyosis: a randomized controlled trial. Acta Obstet Gynecol Scand 2012;91:489–95.
[51] Ferrero S, Gillott DJ, Venturini PL, Remorgida V. Use of aromatase inhibitors to treat endometriosis-related pain symptoms: a systematic review. Reprod Biol Endocrinol 2011;9:89.
[52] Stegeman BH, de Bastos M, Rosendaal FR, van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. BMJ 2013;347:f5298.
[53] Hansen KA, Chalpe A, Eyster KM. Management of endometriosis-associated pain. Clin Obstet Gynecol 2010;53:439–48.
[54] Winkel CA. Evaluation and management of women with endometriosis. Obs Gyn 2003;102:397–408.
[55] Lindh I, Milsom I. The includence of intrauterine contraception on the prevalence and severity of dysmenorrhea: a longitudinal population study. Hum Reprod 2013;28:1953–60.
[56] Kauffman RP. Review: levonorgestrel IU system, OCPs, and antifibrinolytics each reduce bleeding in endometrial dysfunction. Ann Intern Med 2013;159:JC10.
[57] Matteson KA, Rahn DD, Wheeler 2nd TL, Casiano E, Siddiqui NY, Harvie HS, et al. Nonsurgical management of heavy menstrual bleeding: a systematic review. Obstet Gynecol 2013;121:632–43.
[58] Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E, Silva JC, Podgaec S, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod 2005;20:1993–8.
[59] Hayden C. GnRH analogues: applications in assisted reproductive techniques. Eur J Endocrinol 2008;159(Suppl. 1):S17–25.
[60] Cheng MH, Chao HT, Wang PH. Medical treatment for uterine myomas. Taiwan J Obstet Gynecol 2008;47:18–23.
[61] Cheng MH, Wang PH. Uterine myoma: a condition amendable to medical therapy? Expert Opin Emerging Drugs 2008;13:119–33.
[62] Wang PH, Lee WL, Cheng MH, Yen MS, Chao KC, Chao HT. Use of a gonadotropin-releasing hormone agonist to manage perimenopausal women with symptomatic uterine myomas. Taiwan J Obstet Gynecol 2009;48:133–7.
[63] Hirata JD, Moghissi KS, Ginsburg KA. Pregnancy after medical therapy of adenomyosis with gonadotropin-releasing hormone agonist. Fertil Steril 1993;59:444–5.

[64] Nelson JR, Corson SL. Long-term management of adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril 1993;59:441–3.
[65] Silva PD, Perkins HE, Schauberger CW. Live birth after treatment of severe adenomyosis with a gonadotropin-releasing hormone agonist. Fertil Steril 1994;61:171–2.
[66] Huang FJ, Kung FT, Chang SY, Hsu TY. Effects of short-course buserelin therapy on adenomyosis. A report of two cases. J Reprod Med 1999;44:741–4.
[67] Lin J, Sun C, Zheng H. Gonadotropin-releasing hormone agonists and laparoscopy in the treatment of adenomyosis with infertility. Chin Med J (Engl) 2000;113:442–5.
[68] Guo SW, Olive DL. Two unsuccessful clinical trials on endometriosis and a few lessons learned. Gynecol Obstet Invest 2007;64:24–35.
[69] Richardson AR, Maltz FN. Ulipristal acetate: review of the efficacy and safety of a newly approved agent for emergency contraception. Clin Ther 2012;34:24–36.
[70] Santos M, Hendry D, Sangi-Haghpeykar H, Dietrich JE. Retrospective review of norethindrone use in adolescents. J Pediatr Adolesc Gynecol 2014;27:41–4.
[71] Savasi I, Jayasinghe K, Moore P, Jayasinghe Y, Grover SR. Complication rates associated with levonorgestrel intrauterine system use in adolescents with development disabilities. J Pediatr Adolesc Gynecol 2013;27:25–8.